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REMARKS

Claims 14-20 and 25-31 were pending. No claim has been allowed. Claim 14 is amended herein. Support for the amendment to claim 14 is found in the specification at page 5, line 2. Therefore, it is believed that no new matter has been added. Claims 14-20 and 25-31 are currently pending.

Formal Matters

Applicants gratefully acknowledge the withdrawal of the rejections under 35 U.S.C. § 112.

Rejection Under 35 U.S.C. § 102 (e)

Claims 14, 15, 17, 19, 20, and 25-27 are rejected under 35 U.S.C. § 102 (e) as allegedly being anticipated by Burmer, U.S. Patent 6,087,103. According to the Action, Burmer discloses a method and kit to screen a plant extract for compounds (ligands), *i.e.*, small organic molecules, that bind selectively to a target protein wherein a crude plant extract is fractionated (separated by gradient density centrifugation) to obtain fractions. The Action asserts that the fractions containing the compounds each have a different location or ligand address that are identified by reference to matrix on a solid support are disclosed as well as detectable moieties. Applicants traverse this rejection.

Applicants respectfully submit that each and every element of the claimed methods are not disclosed in Burmer, and therefore Burmer does not anticipate the methods.

1. **Burmer does not disclose the use of plant fractions.**

The disclosure in Burmer does not teach or suggest the fractionation of plant extracts in its disclosure of nucleic acid isolation because fractionation and isolation are distinct processes. Fractionation is the process by which different components in a complex mixture are separated based on one or more chemical properties of the components. Such properties include molecular size and charge. Thus, fractionation results in a series of fractions with components having some similarity in the chemical properties used for fractionation. On the other hand, isolation is the process by which a single, defined component is separated or removed from a complex mixture.

Because fractionation and isolation are distinct in both the principle and the purpose of the process, the disclosure of one process does not teach or suggest the other.

Burmer, in fact, only discloses the isolation of nucleic acids from plants. While the Action asserts that Burmer discloses the use of plant fractions in column 8, lines 12-65, the section discloses only isolation techniques. This section in the Burmer specification is entitled "Preparation of Nucleic Acid Libraries Encoding Tags, Ligands, and Targets." *See* column 8, lines 12-13. In this section, Burmer describes general recombinant nucleic acid methods, *e.g.*, cloning and sequencing, as well as methods for isolating nucleic acids. Burmer mentions plants as a source of nucleic acids at column 8, line 45. However, Burmer does not describe, mention, or intone any fractionation of plant extracts into different fractions for analysis in this section. Similarly, the fractionation of plant extracts is not disclosed or even mentioned at column 15, lines 8-24. Therefore, plant fractions are not disclosed or suggested in Burmer, resulting in at least one of the claimed elements of independent claims 14 and 25 being completely absent from Burmer.

2. Burmer does not teach or disclose a method involving fractionation followed by a further selection step requiring ligand interactions with a single labeled target.

The invention of the instant methods lies in the method of selection employed. In other words, the instant invention makes use of differences in size and charge of the molecules within the extract as well as differences in ligand binding properties to identify potentially useful molecules in plant extracts. Specifically, the instant methods fractionate crude plant extracts, a first selection based on differences in size and charge, and then subject these fractions to a second selection step requiring that a ligand in the fractionated extract complex with a labeled target, a second selection based on ligand-binding properties.

Burmer does not teach or disclose such a method. First, as discussed above, the methods of Burmer do not require a first fractionation step. At best, Burmer requires isolation of nucleic acids in some embodiments. Second, Burmer discloses a selection method distinct from the methods of the instant application.[1] Burmer always employs a multitude of tagged targets (or ligands), and not a single target (or ligand). For example, in the description under the Field of Invention, Burmer states that "the present invention relates to screening methods that can readily be used to identify

[1] Applicants note that the terms "target" and "ligand" are arbitrarily assigned. In Burmer, the ligand is the tagged substrate, while in the instant application, the target is the tagged substrate.

simultaneously multiple proteins or compounds that interact with multiple ligands using a tagged array of ligands." *See* column 1, lines 17-21 (emphasis added). The assay is again described as one using multiple ligands at column 1, line 61 - column 2, line 5, where the specification states that the method comprises "incubating a target with at least two tagged ligands." Again, at column 2, lines 34-53, the specification discloses the use of "incubating an expressed cDNA library of target proteins with the pooled tagged ligand proteins" (emphasis added). In fact, Burmer discloses the use of multiple tagged ligands throughout the specification. *See, e.g.*, column 3, lines 20-24 and lines 63-64; column 16, lines 15-23, and Claim 1, step d. Simply stated, Burmer describes a method where targets are immobilized at a particular addresses in matrix. The matrix of single targets is then subjected to a pool of at least two tagged ligands, which are, in turn, identified by their tags. In contrast, the instant methods employ individual fractions immobilized at a particular address in the matrix. The multitude of fractions is then subjected to a single tagged compound in order to identify which fractions react with the compound, not to identify which of many compounds react with any fraction.

For these reasons, the instant methods are distinct from those of Burmer, and therefore are not anticipated by Burmer. Applicants respectfully submit that the rejections under 35 U.S.C. § 102(e) have been overcome. Accordingly, the basis for this rejection may be withdrawn.

Rejection Under 35 U.S.C. § 103 (a)

Claims 16, 29 and 30 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Burmer in view of Baek or Verma. According to the Action, Burmer teaches a method and kit to screen a plant extract for compounds that selectively bind to a target protein wherein a crude plant extract is fractionated to obtain fractions. Baek discloses extracting and fractionating compounds from *Carthamus tinctorius* using silica gel column chromatography. Verma teaches extracting and isolating *Carthamus tinctorius* with antithrombotic capacity. Claims 18 and 28 are rejected under 35 U.S.C. § 103(a) at unpatentable over Burmer in view of Kutsuna. The Action asserts that Kutsuna discloses the isolation, identification, and determination of biologically active compounds from safflower *Carthamus tinctorius*. Claim 31 is rejected under 35 U.S.C. § 103(a) as unpatentable over Burmer in view of Baek or Verma, as applied to claims 16, 29, and 30, and in further view of

Kutsuna. Applicants traverse this rejection.

1. The cited combination of references does not result in the instant methods.

Applicants respectfully submit that the combined references do not teach or suggest all the claim limitations, and therefore the combination fails to result in the claimed methods. As discussed above, Burmer does not teach or suggest a method to screen plant extracts using a fractionation step followed by a further selection step requiring ligand interactions with a single labeled (or tagged) target. Baek, Verma, and Kutsuna do not remedy this deficiency in Burma. Baek and Kutsuna rely on a single extraction step to isolate compounds. Baek has no teaching regarding additional steps after the fractionation useful in identifying compounds. Kutsuna teaches only the use of nuclear magnetic resonance to identify compounds following fractionation of plant extracts. Verma reviews the chemistry and biology of *Carthamus tinctoris*. Verma has no teaching or suggestion as to how to identify compounds in *Carthamus tinctoris* or, for that matter, other plants. In sum, neither Baek, Verma, nor Kutsuna teach or suggest the use of target-binding properties to identify compounds in plant extracts. Therefore, the combination of Burmer with Baek or Verma in view of Kutsuna fails to result in the claimed methods. As a case of *prima facie* obviousness requires that the combined references result in the claimed methods, the absence of such teachings renders the claimed methods nonobvious.

2. The references do not provide a motivation or suggestion to combine or modify the references.

There is no motivation or suggestion to combine these references to use a single labeled (or tagged) target to identify compounds in immobilized plant extracts. "There must be some suggestion for [combining prior art references] found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art." *In re Jones,* 21 U.S.P.Q.2d 1941, 1943-44 (Fed. Cir. 1992). Burmer does not suggest the use of plant extracts. Both Baek and Kutsuna lack any suggestion that modification of the disclosed methods are required to identify compounds, while Verma lacks any suggestion whatsoever regarding the identification of such compounds. In fact, the successful identification of some compounds using the methods of Baek and Kutsuna teaches away from the need to use any additional steps to identify such compounds. Hence, the combination of these references is improper and does not support the obviousness rejection.

3. The references fail to provide a reasonable expectation of success.

Applicants respectfully submit that the identification of compounds by the methods of the combined references does not render the success of the present methods obvious to the skilled artisan. While it is recognized that plants have significant chemical diversity in its resident compounds, this does not automatically correspond to useful biological and/or therapeutic activity. *See, e.g.*, Exhibit A. Furthermore, high throughput screening of plant extracts differs in technologically meaningful ways from screening of purified protein or nucleotide libraries of, *e.g.*, Burmer. Natural product extracts typically are colored, insoluble, and consists of numerous products that may interact (either synergistically or antagonistically), result in false positives, and present significant challenges in assay sensitivity. *See, e.g.*, Exhibit B. Therefore, a method screening purified libraries does not provide any expectation of success for a method screening natural product extracts.

In light of the above, Applicants respectfully submit that the rejections under 35 U.S.C. § 103(a) have been overcome. Therefore, the basis for this rejection may be withdrawn.

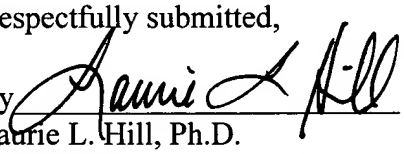
CONCLUSION

Applicants submit that the rejections under 35 U.S.C. §§ 102 and 103 have been overcome by the above remarks. Early allowance of pending claims 14-20 and 25-31 is respectfully requested. If the Examiner thinks an telephonic conference would be helpful, please call the undersigned at (858)720-7955 at your convenience.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 205032000400. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 7, 2003

Respectfully submitted,

By 

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